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09/937,991	01/23/2002	Hirofumi Yura	33944	8819

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,991	YURA ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3 and 6-16 have been presented for examination. Claim 5 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim1-3 and 6-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1and 7 recite that X, Y and Z denotes any substituent group. It is not clear what substituents are included by this recitation. In the absence of the specific moieties intended to effectuate modification by "substitution" or attachment to the chemical core claimed, the terms "any substituent" renders the claims in which it appears indefinite in all occurrences wherein applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicant regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

Claim 1 is drawn to a functionalized polymer and recites that n, which denotes the number of repeating units of formula (1) is at least 1. This means that n can be 1 or more. If n is 1 then the resulting structure is not a functionalized polymer, but a functionalized monomer. When n is 2-4 it is defined as an oligomer (American Heritage Dictionary of the English Language, Fourth Edition, 2000). Hence it is a polymer only when n>4. The claim recitation is

not clear. For the purpose of prosecution it is interpreted that applicants are claiming the compound of structural formula (1) wherein n is any integer equal to 1 or greater than 1.

The term "partially" in claims 8-10 is a relative term that renders the claim indefinite. The term "partially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Any percentage less than a 100% desulfation will be considered as partial.

Claim 6 recites a cell growth control agent characterized by containing a functionalized polymer in accordance with any one of claims 1-3. It is not clear if applicants intend the structural formula (1) as a whole is a cell growth control agent or if one of the substituents attached to the main chain in formula (1) is a cell growth control agent or if a discrete cell growth control agent is in combination with the polymer of structural formula (1). For the purpose of prosecution it is interpreted as any one of the above.

Claims 7-10 recite, "An agent comprising". It is not clear what applicants intend by this recitation. The recitation is interpreted as a composition comprising the said functionalized polymer and any other chemical moiety either as a mixture or as a conjugate or just the functionalized polymer having formula 7.

Claim 9 recites heparin/heparan sulfate. It is not clear what applicants intend by the manner in which this recited. This is interpreted to mean either the individual gycosaminoglycan or a mixture of the two. Clarification is needed.

Claims that depend from rejected base claims that are unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

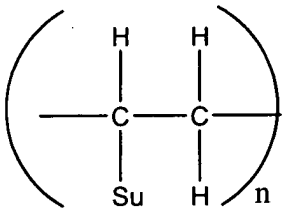
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 7-16 are rejected under 35 U.S.C. 102(b) as being anticipated individually by Tay et al (Biomaterials, 1989, Vol. 10(1), pp 11-15) and Larsson et al (WO 93/05793).

Tay et al disclose the coupling of heparin to the hydroxyl group of polyvinyl alcohol (page 13, section entitled "Coupling of Heparin to Hydrogels). This will produce a structure as shown below:



wherein Su is the heparin moiety. In this polymer the starting polyvinyl alcohol has a molecular weight of 43000 (page 12, left column, see under materials and methods), which corresponds to 977 repeat units (n=977; repeat unit of polyvinyl alcohol has a molecular weight of 44). The molecular weight of the heparin used is 7000 (page 13, left column, first paragraph). The repeat unit of heparin has a molecular weight of approximately 576, which corresponds to a chain comprising 12 repeat units in the heparin chain (denoted by Su in the structure above). This meets the limitation of instant claims 1-3, 7-10,13, 15 and 16. Claim 1 requires that n be atleast 1. Tay's functionalized polymer has n>1.How the carbohydrate chain is obtained as recited in

instant claims 2 and 13 is not given patentable weight since the claim is a product by process claim and such a product is limited only by the structure and not by the process steps. This teaching also meets the limitation of claim 14 since it is apparent that the carbohydrate moiety will have the morphology as recited in claim 14, i.e. in solution the carbohydrate unit will be spread out from the main core, which is the polyvinyl chain since it has 12 repeat units which is bulky enough to be spread out and not exist in any other manner. Since the main chain is derived from polyvinyl alcohol, this also constitutes a functionalized polymer wherein the main chain is a vinyl polymer. This meets the limitation of claim 11.

Larsson et al disclose a conjugate comprising a straight chain organic homo- or heteropolymer having a number of functional groups distributed along the polymer backbone, which have groups of at least 20 molecules of sulfated glycosaminoglycans are anchored through covalent bonds. The glycosaminoglycans comprise heparin, heparan sulfate, dermatan sulfate, chondroitin sulfate and fragments and derivatives of these substances (page 7, lines 5-35; page 21, example 7; pages 26-28, claims 1-5, 7-12 and 18).

These disclosures of Tay and Larsson are seen to meet the limitations of claims 1-3 and 7-16. The recitation in claims 2 and 8 as to how the carbohydrate chain is obtained is not given patentable weight.

Claims 7-10, 12, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Joh (US 4415490).

Claims 7-10 are drawn to an agent comprising a functionalized polymer of structural formula (1); wherein the glycosaminoglycan is heparin/heparan sulfate, chondroitin sulfate,

dermatan sulfate or partially desulfated modification thereof. Claim 12 is drawn to a functionalized polymer according to claim 1 wherein the polymer main chain is hydrophobic and the carbohydrate chain attached to the polymer main chain is hydrophilic. Claim 15 is drawn to the polymer of claim 7 reciting the limitation of how the polymer is formed. Claim 16 is drawn to the polymer of claim 7 that has morphology in aqueous solution wherein the carbohydrate chain is spread out from the polymer main chain.

Joh drawn to non-thrombogenic materials, teaches a material comprising a base polymer covalently bonded to heparin at each bonding site between the heparin and base polymer. The carbohydrate part of the material is a partly decomposed heparin (a heparinate) molecule bonded to a vinyl chloride-ethylene-vinyl alcohol copolymer (col. 14, example 10). This teaching of Joh is also seen to meet the limitations of claims 7-10, 15 and 16. These claims are drawn to an agent comprising a functionalized polymer of structural formula (1). Since the term agent is not clearly defined by the claim, the material taught by Joh is seen as an agent. Joh teaches that the polymer was washed and then bonded to heparinate. This means that the polymer is hydrophobic. Since an aqueous solution of sodium heparinate was used in making this functionalized polymer the carbohydrate part is hydrophilic. This disclosure is seen to meet the limitations of instant claim 12.

Joint Inventors

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Conrad et al (US 5250519) in combination with Joh (US 4415490).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 6 is drawn to a cell growth control agent characterized by containing a functionalized polymer having the structural formula (1) including the other limitations of any one of claims 1-3.

Conrad et al, drawn to heparin derivatives teach that heparin/heparan sulfate is known to inhibit smooth muscle cell proliferation (col. 1, lines 45-63; col. 2, lines 48 through 64). Conrad

also teaches the use of heparins of his invention for the inhibition of smooth muscle cell proliferation (used as a cell growth control agent, col. 8, lines 18-68; col. 9, line 49 through col. 10, lin 35; col. 14, lines 28-33). However, Conrad et al do not teach a cell growth control agent wherein a glycosaminoglycan like heparin or heparan sulfate is bound to a polymer backbone as recited in instant formula (1) in instant claim 1.

Joh, drawn to non-thrombogenic heparins bound to a polymer teaches that when heparin is bound to a polymer does not dissociate and one does not see any heparin-heparin side reaction nor a polymer-polymer side reaction as is generally seen to a great extent in the art (col. 7, lines 9-16). This means that heparin or any other glycosaminoglycan when bound to a polymer is stable and also not involved in side reactions that reduce their therapeutic effect. However, Joh does not teach the compounds of his invention are cell growth control agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art to covalently bind cell growth control agent like glycosaminoglycans to a polymer backbone as instantly claimed since the use of glycosaminoglycans as cell growth control agents (antiproliferative activity with respect to smooth muscle cells) as well as covalent bonding of glycosaminoglycans to polymers are both taught in the prior art.

One of ordinary skill in the art would be motivated to do so since covalent bonding of glycosaminoglycans to a polymer makes them stable and reduces the involvement of the glycosaminoglycans in side reactions as taught by Joh. This would enhance their therapeutic potential as a cell growth control agent.

Response to applicants Declaration

The declaration by Hirofumi Yura submitted under 37 CFR 1.132 has been considered but is not found to be persuasive. With respect to the rejection of claims 1-3 and 6-11 advanced in the previous office action argue that the PVA used in Tay's teaching is a crosslinked polymer and is rigid and has steric congestion. In addition based on the amounts of reagents used by Tay only a very small percentage off the activated OH groups are substituted by heparin as is instantly claimed. The instant claims require that the functionalized polymer of structural formula (1) wherein the number of repeat units n is atleast 1. In the polymer of Tay even if all of OH groups in the repeat unit of PVA are not substituted by heparin, there is at least one or more than one unit in which the Oh group is substituted by heparin. This is seen to meet the limitations of the instant claims.

This same argument also applies to the argument advanced by the applicant for the rejection of claim 12 as being anticipated by Joh.

Conclusion

Claims 1-3 and 6-16 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached between 8.30am-5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK

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